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P53 TRANSCRIPTION FACTOR AND DIABETES: IS THERE ANY LINK?

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ABSTRACT

Diabetes, a metabolic disorder is alarmingly increasing across the globe and currently ample of research is being carried out to treat hyperglycaemia and its secondary complications in diabetic patients. Despite extensive research, specific causes of this metabolic disorder are still not well understood at molecular level. As p53 a tumor suppressor gene has mostly been associated with cancer, however, the most recent research studies sheds light on vital role of p53 signalling in diabetes development. In this review we underline the role of altered p53 protein expression in diabetes and its associated metabolic disorders including hypertension and dyslipidemia. We try to throw some light on latest studies that suggest how p53 signalling may act as a new potential therapeutic target for diabetes and its related metabolic disorders.

Keywords

P53, Diabetes, Metabolic disorders. Dyslipidemia, theraupetic target

Academic Discipline And Sub-Disciplines

Biochemistry; Molecular Biology

SUBJECT CLASSIFICATION

Chemotheraupetic Molecular Targets

1. INTRODUCTION

At global level, prevalence of diabetes is on frequent rise due to increase in life expectancy, sedentary life style, and obesity. Recently, WHO projects that diabetes will be the 7th leading cause of death in 2030 **(Tesfaye *et al*., 2016).** Global burden of diabetes is so huge that as per the recent International Diabetic Federation (IDF) diabetes atlas, the current number of people with diabetes is 382 million and will rise to 592 million by 2035. In India, at present there are approximately 65.1 million people with diabetes and comes second in number with China representing the world's largest diabetic population i.e.98.4 million **(Laila *et al*., 2016; Adela and Banerjee, 2015).**

Diabetes, a metabolic disorder of multiple aetiologies is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, action or both**.** It is categorized into many types; however, two major types of diabetes are type 1 diabetes and type 2 diabetes **(Craig *et al.,* 2014; Laila *et al.,* 2016).** The causative agents for type 1 diabetes include genetic susceptibility, auto immune, some virus and intra uterine environment whereas, type 2 is often considered to be life style mediated and associated with obesity, high serum level of low density lipoprotein, though role of genetic susceptibility and uterine development can also not be denied **(Joshi and Shrestha, 2010; Laila *et al.,* 2016)**. Despite extensive research, specific causes of this metabolic disorder are still not well understood at molecular level. Although under cellular conditions, several proteins have been reported to exibit their anti-diabetic effects through the transcriptional activation of their target genes, whose regulatory regions contain specific binding sites for them. Among such type of proteins it has been recently reported that Tumor protein P53 plays a pivotal role in diabetes pathogenesis **(Barrio *et al.,* 2014; Yoshida *et al.,* 2015).** The transcriptional activity of p53 is mainly regulated at the posttranslational level. The stability of p53 protein is regulated by several post-translational modifications, including ubiquitination, phosphorylation, acetylation, and sumoylation as well as by its interactions with different cytoplasmic and nuclear proteins, which also alter its activity and function (**Aktary *et al.,* 2013).** Indeed, phosphorylation, acetylation, prolyl-isomerization and sumoylation are the most characterized post-translation modifications of p53 family members that impact on their transcriptional activity either by potentiating or dictating the selectivity in the activation of the proper target gene **(Reismann *et al.,* 2012).** The net result of this selective transcriptional activation is the maximization of the efficacy of its specific cellular effects. Although p53 often acts as a protective factor in cancer, but recent studies shows that it is involved in many other non-cancer diseases including diabetes **(Wu and Wang, 2016).** Though, the role of p53 regulation in diabetes pathological mechanism is not yet clear, but understanding the clear role of p53 signalling mechanism in diabetes pathogenesis may pave way to provide new train of thought for elucidating the pathological mechanism of diabetes development and its proper management. In this review paper an attempt has been made to give the latest insight into the molecular role of P53 in diabetes and various associated disorders.

2. STRUCTURE AND CELLULAR FUNCTION OF P53 TUMOR SUPRESSOR PROTEIN

The basic modular structure of Tumor protein P53 comprises a N-terminal transcriptional activation domain, a central DNA-binding domain and a C terminus with oligomeric and regulatory activities **(George, 2011).** p53 acts as a transcription factor, and previous studies have shown that more than 500 genes are potentially regulated by p53

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(Olovnikov *et al.,* 2008). The p53 protein is a 393 residue polypeptide from N- terminal to C-terminal and contains five functional domains (Figure 1).

Figure 1: P53 Protein structure

These domains regulates its function as a stress-activated sequence-specific DNA-binding protein as well as a transcription factor **(Huart and Hupp, 2013).**The N-terminal domain (residues 1-43) is involved in transcriptional activation, while the basic C-terminal domain (residues 364-393) is a negative regulatory domain that inhibit sequence-specific DNA binding by the core domain. The large, central core domain (residues 100-300) is involved in DNA binding, and is the location of almost all oncogenic p53 mutations **(Jurneczko *et al*., 2013; Freed-Pastor and Prives, 2012).** A proline rich domain (63-97) Mdm2 binds to both N-teminal and C-teminal domains. Additionally, there is an oligomerization domain (residues 320-360) in this protein that contains nuclear localization signals and is involved in p53 tetramerization **(Joerger and Fersht, 2010)**. p53 binds to DNA as a homotetramer with Zinc as cofactor, that binds as a single molecule to each subunit of this protein. At subcellular level, p53 may often be cytoplasmic, predominanltly in its inavtive sate, however, exposure to stress results in its accumulation in the nucleus, where it is expected to exert its biochemical effects **(George, 2011).**The p53 response is tightly controlled and fine-tuned at multiple levels. In the absence of activating signals, p53 is repressed by the oncoproteins including MDM2 and MDM4 (**Hasty and Christy, 2013; Hoffman *et al.,* 2014**). The repressor MDM2 masks the transactivation domain of p53 and it is actually a E3 ligase that targets p53 for ubiquitination wheareas MDM4 lacks E3 ligase activity, but represses the transactivation potential of p53 **(Shi and Gu, 2012**; **Coffill *et al.,*2016**). The tumor suppressor protein p53 has been reported to get activated and stabilized upon cellular stress and various types of genotoxic insults such as ribosomal stress, DNA damage, telomere erosion, nutrient deprivation and oncogene hyperactivation. The p53 tumor suppressor has an important role in gene expression and genetic stability (**Zhang *et al.,* 2014b; Kumari *et al.,* 2014**). As shown in figure 2, diverse signalling pathways converge on the p53/MDM2/MDM4 complex to release p53 from its repressors and enable it to regulate transcription of downstream target genes involved in various cellular responses such s cell cycle arrest, apoptosis, senescence, autophagy, DNA repair and central metabolism **(Allen *et al*., 2014).** After nuclear translocation, p53 acts primarily as transcriptional activator that binds as tetramer to *cis*-regulatory regions of genes. Transactivation by p53 involves the recruitment of general transcription factors (GTFs) of the RNAPII initiation machinery to the core promoter region of target genes **(Gomes and Espinosa, 2010, Albert *et al.,* 2016).** In addition to these, p53 interacts with several other proteins that are involved in subsequent phases of the RNAPII transcription cycle, such as promoter escape or transcription elongation. Moreover, physical interactions of p53 with cyclin-dependent kinase CDK9 have been reported and inactivation of its catalytic activity by small molecule such as flavopiridol (FP) have been found to block mRNA synthesis in living cells, which in turn triggers p53 activation (**Albert *et al*., 2014).**

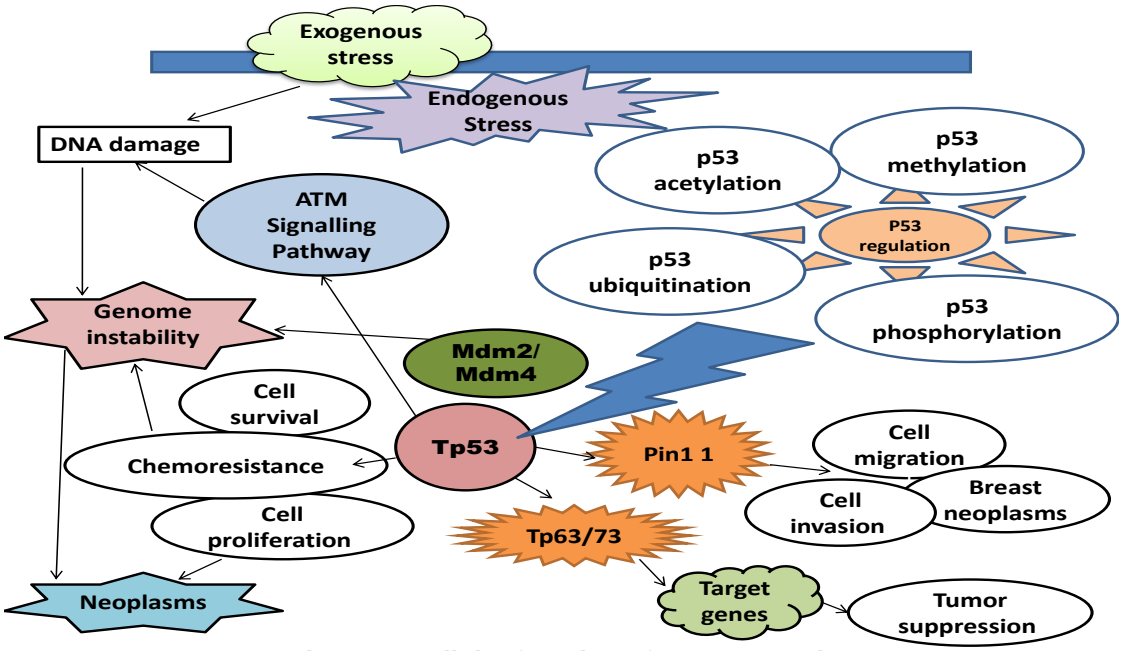

Figure 2: Cellular function of Tumor protein 53

In addition to its anticancer function, p53 has recently been shown (regulated by murine double minute 2/4 oncoprotein, MDM2/ MDM4) to control intracellular metabolic processes (**Wang *et al*., 2013; Berkers *et al.,* 2013**). It participates in the regulation of glucose, fatty and amino acid and purine metabolism, influences mitochondrial integrity and oxidative phosphorylation, insulin sensitivity, antioxidant response and autophagy (**Kuricova *et al*., 2014**). Latest research indicates that p53 also plays a role in cells under non-stress situations and regulate the expression of genes involved in cellular metabolism, such as the cytochrome c oxidase 2 gene (Sco2), glucose transporter genes (including Glut 1 and Glut 4), the phosphoglycerate mutase gene (PGM) and zinc finger protein 385a (Zfp385a, also known as hzf), involved in adipocyte function and glucose homeostasis **(Liang *et al.,* 2013**; **Hager and Gu, 2014**). p53 has been also implicated in the development of insulin resistance through the regulation of senescence in adipose tissue, in autoimmune disease and the macrophage response in a streptozotocin-induced type 1 diabetes mouse model (**Bogazzi *et al*., 2013**). The mice deficient in p53 were found to be more susceptible to streptozotocin-induced type diabetes than wild-type mice and thus suggests p53 had a protective role in this system, however, such type of protective role of p53 in type 2 diabetes and insulin resistance is not yet well established (**Armata *et al.,* 2010).**

3. DYSREGULATED p53/AMP/SIRT1/SEMAPHORIN SIGNALLING IN DIABETES

As the "guardian of the genome," tumor suppressor p53 has been reported to coordinate diverse cellular responses to a broad range of environment stresses and to play antineoplastic roles by activating downstream target genes involved in DNA damage repair, apoptosis, and cell-cycle arrest (**Brady and Attardi, 2010**). Recent studies have indicated broader roles for p53 in mediating metabolic changes in cells under various physiological and pathological conditions especially in glucose homeostasis in diabetes development **(Zhang *et al.,* 2014c).** As shown in figure 3 **u**nder cellular conditions, the expression of Tp53 is variably altered in specific cellular tissues in diabetic condition as well as in associated metabolic disorders.

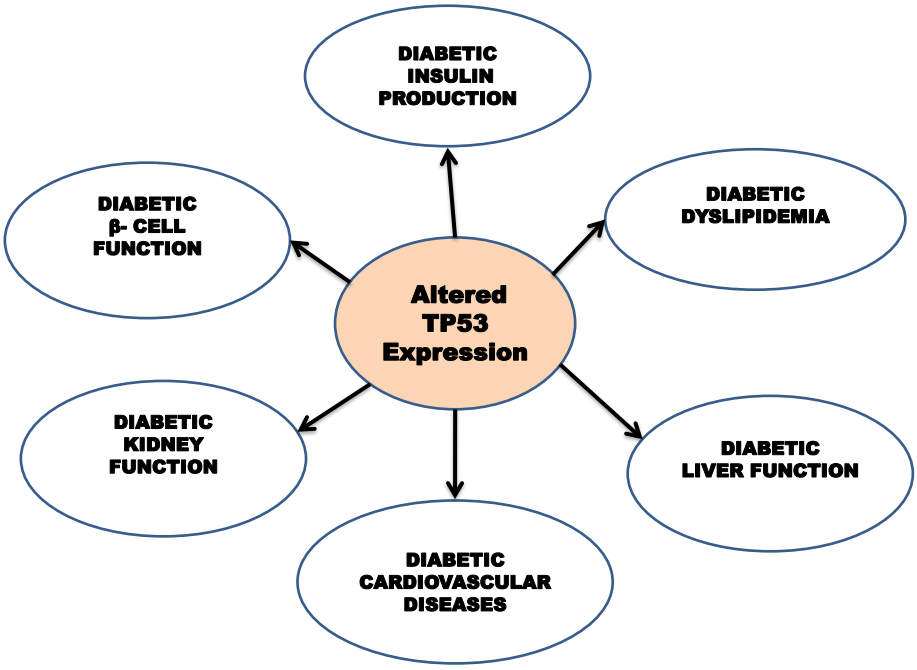

Figure3: Altered Tp53 expression in diabetes

Recently, "Semaphorin" secreted protein encoded by *Sema 3e* gene have been reported to possess chemo attractant activity for inflammatory macrophages in diabetic mice (**Kanasaki *et al.,* 2013; Howangyin and Silvestre, 2014**). Semaphorin being one of the targets of p53 have been found to be elevated in the blood of diabetic patients and thus inhibition of p53/Semaphorin signalling may be a new therapeutic option for diabetes **(Yoshida *et al.,* 2015).**.

A more recent research by **Kung *et al* (2016)** demonstrated a single nucleotide polymorphisms (SNPs), or variations at single points in a DNA sequence of p53 linked with obesity and metabolic diseases. In two mice variants it was found that the most common SNP in p53 occurs at amino acid 72, encoded by nucleotide sequence that codes for one of two amino acids namely Proline (P72) or Arginine (R72). **Kung and his co workers (2016)** further identified the two genes (*Npc1l1 and Tnf*) controlled by p53 noticeably different in the livers of the R72 mice as compared to P72 mice. *Npc1l1* gene has been linked to cholesterol absorption while *Tnf* is associated with obesity-induced insulin resistance. These genes were found to act as "early-responders" to a high-fat diet and helped initiate the development of obesity and non-alcoholic fatty liver disease in the R72 mice. Drugs that specifically inhibit these two genes led to significant decreases in weight gain and fat accumulation in R72 mice. It is clear that targeting *Npc111* and *Tnf* may be effective strategies for the treatment of diabetes.

One of the important p53 target, ATM protein kinase mutated in A-T patients (Atm), has been implicated in metabolic disease characterized by insulin resistance, increased cholesterol and lipid levels, blood pressure, and atherosclerosis (**Stracker *et al.,* 2013**). ATM phospshorylates the p53 tumor suppressor on a site (Ser15) that regulates its transcription activity (**Loughery *et al.,* 2014**). **Armata *et al*** (2010) examined insulin sensitivity in mice with a germ line mutation that replaces the p53 phosphorylation site with alanine and the loss of p53 Ser18 (murine Ser15) led to increased metabolic stress, including severe defects in glucose homeostasis and the mice developed glucose intolerance and insulin resistance. The insulin resistance correlated well with the loss of antioxidant gene expression and decreased insulin signalling. Thus it is clear p53 phosphorylation on an ATM site is an important mechanism in the physiological regulation of glucose homeostasis (**Ambrose and Gatti, 2013**).

4. p53 IN DIABETIC β- CELL FUNCTION

The appreciation of the pancreatic β-cell as a central player in the pathogenesis of both type 1 and type 2 diabetes has renewed focus on ways to improve glucose homeostasis by preserving, expanding and improving the function of this key cell type **(Vetere *et al.,* 2014).** In islet β cell, cytoplasmic p53 induces mitochondria dysfunction and impaired insulin secretion as a result of which it promotes diabetes development (**Wali *et al.,* 2013**). β -cells regulate glucose serum levels by means of production and excretion of insulin **(Whaley *et al.,* 2012)**. Although the precise mechanism of glucotoxicity on the β-cells is not fully known, several mechanisms have been proposed, and the most outstanding being: the increase of Reactive Oxygen Species (ROS), the loss of the mitochondrial membrane potential, and the activation of the intrinsic route of the apoptosis due to p53 (**Bensellam *et al.,* 2012**).The elimination of p53 occurs in the proteasome, and depends on its ubiquitination by Murine Double Minute 2 (Mdm2) (**Manfredi, 2010**). Hyperglycemia affects the concentration, ubiquitination and phosphorylation of Mdm2, as well as the phosphorylation of p53, and thus affecting its average life. **Camarillo and his co workers (2015)** demonstrated that the high blood glucose levels promotes the interaction between p53 and Mdm2 while as the ubiquitination of p53 diminishes it. Thus, it is likely that hyperglycemia interferes with the capacity of Mdm2 to ubiquitinate p53, and its degradation, which allows p53 to move towards the mitochondria to activate intrinsic route of the apoptosis (**Kon *et al.,* 2012**). Other alterations caused by hyperglycemia such as Poly (ADP-ribosylation), and O-GlcNAc also contribute to p53 stabilization and activation (**Zheng *et al.,* 2016**). Thus knowing what mechanisms activate the death of the pancreatic β-cells, will allow proposing alternative treatment to prevent dysfunction and decreased mass of pancreatic β-cells.

In one of the study it was revealed that membrane depolarization via KATP channels, calcineurin signaling, DNA breaks, and p53 as determinants of β-cell glucotoxicity and suggest a pharmacological approaches to enhance β -cell survival in diabetes (**Tornovsky-Babeay *et al.,* 2013)**. While studying the dynamics of pancreatic β-cell mass for developing strategies to treat both type 1 and type 2 diabetes, it was found that transgenic mice with an ectopic p53 gene encoding Delta40-p53 developed hypoinsulinemia and glucose intolerance by 3 months of age, which worsened in older mice and led to overt diabetes and premature death from 14 months of age **(Hinault *et al.,* 2011)**. Thus a novel role of Delta40-p53 in β-cell proliferation with implications for the development of age-dependent diabetes was exploited for future studies as novel theraupetic target.

5. p53 IN DIABETIC INSULIN PRODUCTION

Insulin, a major hormone secreted from pancreatic *β* cells regulates the glucose homeostasis. The secretion of insulin from *β* cells is a complex process involving the integration of multiple stimuli (such as nutrients, hormones, neurotransmitters, and drugs) that alter the expression of several target gene products **(Gong and Muzumdar, 2012).** In recent research to investigate the role of islet p53 it was found that genetic and pharmacological inhibition of p53 preserves insulin secretion and glucose tolerance in both streptozotocin-induced type 1 and db/ db mouse models of type 2 diabetes **(Hoshino *et al* 2014)**. It was seen that glucolipotoxicy induces accumulation of islet p53 in the cytosol via oxidative stress and endoplasmic reticulum stress that in turn, inhibited the autophagic clearance of damaged mitochondria by an inhibitory protein–protein interaction with a protein namely parkin, leading to the impairment of mitochondrial energetics and subsequent insulin secretion signals in islet β-cells. In another study conducted by **Minamino *et al* (2009),** it was observed that p53 expression in adipose tissue is crucially involved in the development of insulin resistance, which underlies age-related cardiovascular and metabolic disorders including diabetes. Inhibition of p53 activity in adipose tissue markedly ameliorated senescence-like changes, decreased the expression of proinflammatory cytokines and improved insulin resistance in mice with type 2 diabetes and conversely, upregulation of p53 in adipose tissue caused an inflammatory response that led to insulin resistance. The above observations clearly indicate that results show a previously unappreciated role of adipose tissue p53 expression in the regulation of insulin resistance and suggest that cellular aging signals in adipose tissue could be a new target for the treatment of diabetes. Further, **Bonfigli *et al* (2013)** that p53 codon 72 (Arg72Pro) polymorphism influences insulin resistance in type 2 diabetic patients independently of body mass. As there are several reports that indicates, insulin resistance prevalent among patients with heart failure, but without knowing the exact mechanism. However, **Shimizu *et al* (2012)** reported in insulin resistance associated heart failure the upregulation of p53 was found to be in adipose tissue of patients. They found that pressure overload markedly upregulated p53 expression in adipose tissue along with an increase of adipose tissue inflammation as well as chronic pressure overload accelerated lipolysis in adipose tissue. Further, it was found that in the presence of pressure overload, inhibition of lipolysis by sympathetic denervation significantly downregulated adipose p53 expression and inflammation, thereby improving insulin resistance (**Ortega *et al.,* 2014**). In nutshell it indicate that chronic pressure overload up regulates adipose tissue p53 by promoting lipolysis via the sympathetic nervous system, leading to an inflammatory response of adipose tissue and insulin resistance.

6. p53 IN DIABETIC CARDIOMYOPATHY

Diabetic cardiomyopathy is characterized by energetic dysregulation caused by glucotoxicity, lipotoxicity, and mitochondrial alterations attributed to oxidative stress signalling and oxidative stress-related responses that ultimately lead to cardiovascular remodeling, atherogenesis and organ damage. Recently, **Caamaño (2011)** investigated established that Pro72Arg polymorphism of the *TP53* gene is associated with CAD in Chilean individuals. **Nakamura *et al* (2012) reported that** cardiac expressions of p53 and cytochrome c oxidase 2 in STZ induced diabetic and db/db mice were significantly unregulated as compared to control group, resulting in marked decrease in cardiac performance. As compared to control there was increased mitochondrial oxygen consumption that was in parallel with augmentation of mitochondrial cytochrome c oxidase (complex IV) activity. Further, reactive oxygen species (ROS)-damaged myocytes and lipid accumulation were increased in association with membrane-localization of fatty acid translocase protein FAT/CD36 **(Guzzardi and Iozzo, 2011; Martius *et al*., 2015).** However, the antioxidant tempol was found to reduce the increased expressions of p53 and cytochrome c oxidase in diabetic mice hearts and normalized alterations in mitochondrial oxygen consumption, lipid accumulation, and cardiac dysfunction. In nutshell it was found that myocardial p53/ cytochrome c oxidase 2 signal is activated by diabetes-mediated ROS generation to increase mitochondrial oxygen consumption, resulting in excessive generation of mitochondria-derived ROS and lipid accumulation in association with cardiac dysfunction. High ACE levels are considered as major risk factor for cardiovascular disease, but little is known about the molecular mechanisms regulating ACE expression in endothelial cells. **Kohlstedt *et al* (2013)** determined the role of the AMPK and the miR-143/145-cluster playing a key role in regulating ACE expression in different cell types and are activated/upregulated in response to shear stress. Since p53 an AMPK target, regulates miRs at the transcriptional and post-transcriptional levels and shear-stress elicit the AMPKα2-mediated phophorylation of p53 (Ser15). It was reported that suppression of p53 (siRNA) decreased miR-143/145 levels, increased endothelial ACE expression and prevented its shear stress-induced downregulation (**Hu *et al.,* 2014**).

7. p53 IN DIABETIC DYSLIPIDEMIA

Diabetes is often associated with dysregulation of metabolism of lipids leading to dyslipidemia**.** Several research reports suggest that the ideal treatment of diabetes, in addition to glycaemic control, should have a favourable effect on lipid profiles **(Laila *et al* 2016).**Recent studies suggest that p53 is capable of much broader cellular functions, including the regulation of energy metabolism and autophagy. However, the role of p53 in regulating lipid metabolism is less well understood. In a recent research study by **Wang *et al* (2012),** it was proposed that deficiency of p53 leads to down regulation of aromatase expression (enzyme that converts androgens to estrogens) as well as its activity. This phenomenon in turn, results in the elevated levels of serum testosterone and the increased ratio of Testosterone (T)/ Prostagalndin (17β-oestradiol, E2) that ultimately leads to promotion of lipid accumulation in both mouse embryonic fibroblast (MEF) cells and mouse liver **(McInnes *et al.,* 2012)**. Therefore it is clear that p53 in negatively regulating lipid accumulation and it is conceivable that p53 may act as a potential therapeutic target for various lipid metabolic disorders, such as obesity, diabetes, and liver steatosis.

8. p53 IN DIABETIC KIDNEY FUNCTION

p53 has been reported to regulate multiple signalling pathways in the development of diabetic kidney diseases. It is suggested that there is a glucose-induced acute kidney injury. Recently, **Peng *et al* (2015)** demonstrated that severity of acute kidney injury in the mice was found to correlate well with their blood glucose levels and under *in vitro* conditions, high glucose-conditioned renal proximal tubular cells showed higher apoptosis and caspase activation following ATP-depletion and hypoxic injury, accompanied by a heightened mitochondrial accumulation of Bax and release of cytochrome c (**Allison *et al.,* 2014**). In response to injury, both glucose-conditioned renal proximal tubular cells and diabetic kidney tissues showed markedly higher p53 induction and suppression of p53 was found to diminish the sensitivity of high glucose-conditioned cells to acute injury *in vitro* (**Ozkok and Edeistein, 2014**). Moreover, blockade of p53 by pifithrin-α, siRNA, or proximal tubule-targeted gene ablation reduced ischemic acute kidney injury in diabetic mice (**Zhang *et al.,* 2014a**). Besides, p53 and microRNAs (miRNAs) may regulate transforming growth factor-β1 (TGF-β1) expression in diabetes mice to affect the development of diabetes renal fibrosis (**Kato and Natarajan, 2012**). Although few reports indicate p53/miRNAs signalling may participate in a variety of signaling pathways regulating kidney inflammation and fibrosis to control diabetic kidney disease pathological development. However, the smechanism of this signalling pathway participating in diabetic kidney diseases pathological development is not yet clears **(Wu and Wang, 2016).**

9. p53 IN DIABETIC LIVER FUNCTION

The liver has an important role in carbohydrate metabolism since it is responsible for the balance of blood glucose levels by means of glycogenogenesis and glycogenolysis (**Moore *et al.,* 2012**). In the presence of hepatic disease, the metabolic homeostasis of glucose is impaired in diabetes and associated metabolic disorders **(Garcia-Compean *et al.,* 2009).** Recently, several studies found that p53 regulates primary metabolic pathways both as part of its antitumor role and as a protein responsible for maintaining glucose homeostasis (**Wang *et al.,* 2013**). In a research study, rodents fed with a high-fat, high-sucrose diet or with obesity, the protein abundance of p53 in the liver was elevated, whereas AMPK and SIRT1 were downregulated (**Vila *et al.,* 2014; Nelson *et al.,* 2012)**. In another study, p53 was reported to induce a set of gluconeogenic genes and genes regulating the supply of gluconeogenesis precursors in cultured primary hepatocytes and hepatocytes lacking p53 were observed with impaired glucose production **(Goldstein and Hager, 2015).** However, in diabetic condition, hyperglycaemia increases p53 expression via inhibiting AMPK/SIRT1 signalling pathways in liver cells, which causes lipid accumulation and insulin resistance (**Violett *et al.,* 2012; Hashiramoto and**

Kaku, 2012). Using metformin to activate high glucose-inhibited AMPK/SIRT1 signalling pathway was found to reasonably decrease the expression of p53 protein however over-expressed p53 reduced the expression of SIRT1 protein and inhibits metformin-activated AMPK signaling, accompanied by the decrease of triglycerides **(Wu and Wang, 2016).** Human hepatoma (HepG2) cells exposed to high glucose concentrations that have been shown to inhibit AMPK and SIRT1, induce lipid accumulation, and cause insulin resistance and, activation of AMPK and SIRT1 by metformin results in decreased p53 protein abundance(**Nelson *et al.,* 2012)**. The overexpression of p53 decreased SIRT1 abundance and diminished the ability of metformin both to activate AMPK and to decrease cellular triglycerides. These findings suggest the existence of a reciprocal relationship between hepatic AMPK-SIRT1 signaling and p53 protein under conditions of nutrient excess and in response to metformin.

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